Tamoxifen and CYP2D6:

PGRN/TBCI Summit

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Current Applications of Pharmacogenomics in Breast Cancer

- How did we get to this point?
- Tamoxifen and pre-clinical models
- Basic principles of biomarker discovery and validation
- Future directions

What do our patients want?

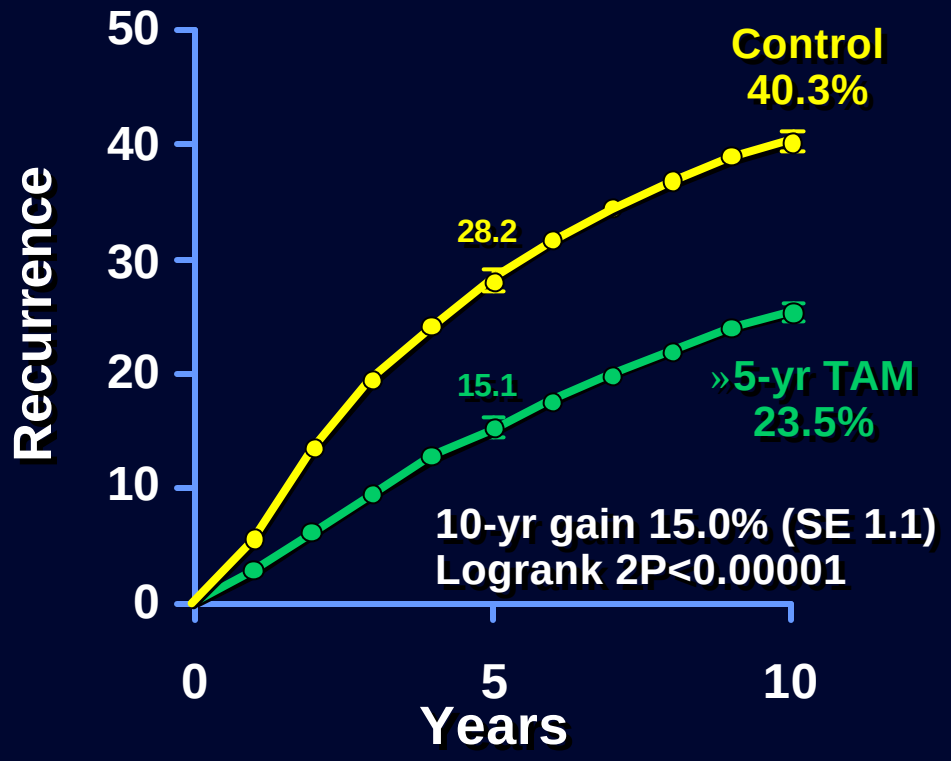
- **Individualized therapy:** The right drug at the right dose
- Up until now, individualized therapy in breast cancer has NOT been synonymous with “pharmacogenetics”

Breast Cancer and Chemotherapy: General principles

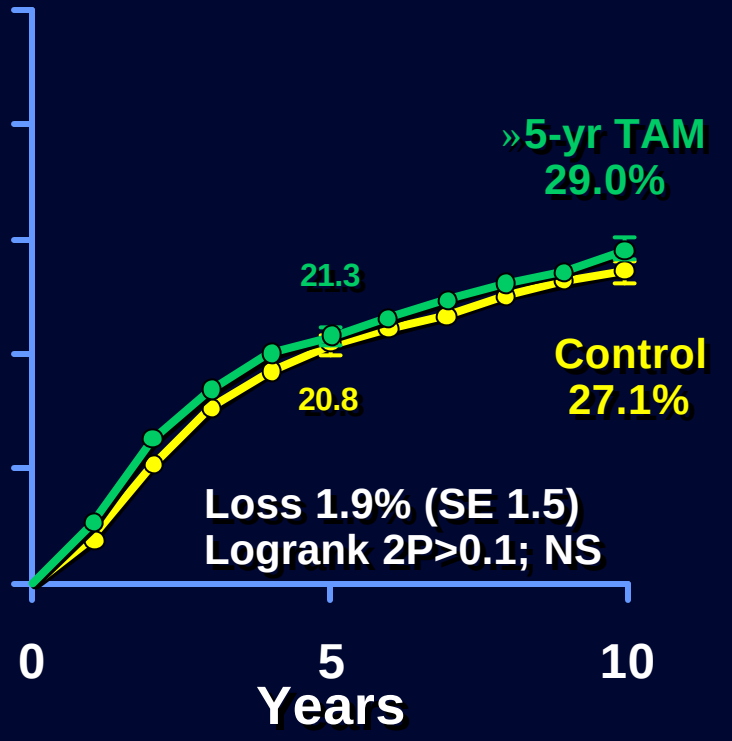
- Chemotherapy will cure cancer
- Oncologists have been trained to treat toxicity—not prevent it
- If treatment doesn’t work, just give more
- No need to worry about toxicity, just provide supportive care (e.g. G-CSF)

Oxford Overview: 5 Years of Tamoxifen vs Not
ER Positive vs ER Negative

»5 Years Tamoxifen vs Not
Recurrence
ER+/ER Unknown
Entry age ³50



»5 Years Tamoxifen vs Not
Recurrence
ER – Poor PR – Poor



"Of Mice and WoMen": Tamoxifen Metabolism

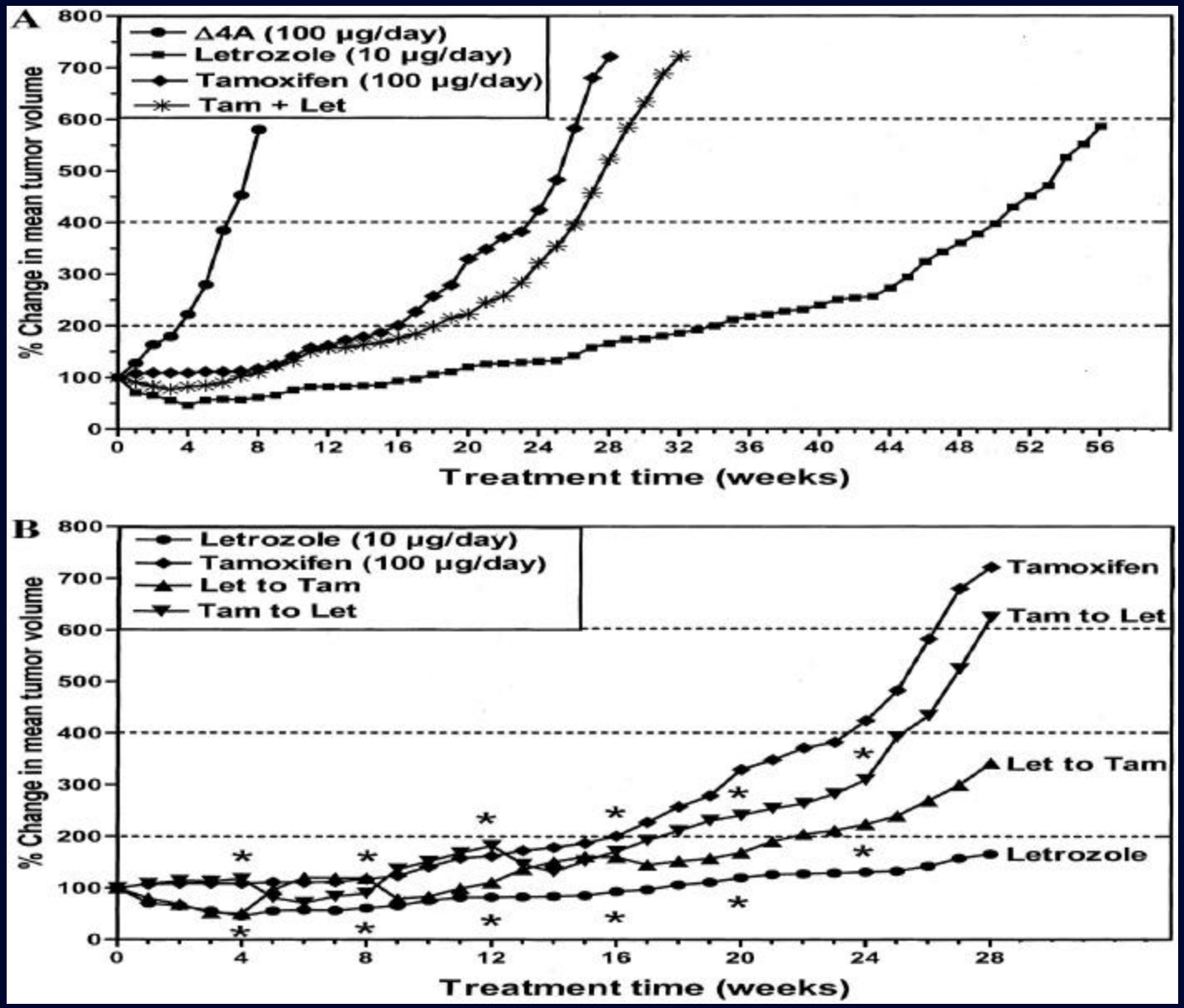
- Were the clinical findings predicted by pre-clinical models?
- Why should oncologists care about pharmacology and/or pharmacogenetics?

Therapeutic Strategies Using the Aromatase Inhibitor Letrozole and Tamoxifen in a Breast Cancer Model

Brian J. Long, Danijela Jelovac, Venkatesh Handratta, Apinya Thiantanawat, Nicol MacPherson, Joseph Ragaz, Olga G. Goloubeva, Angela M. Brodie

Journal of the National Cancer Institute 2004 96(6):456-465

Effects of letrozole and tamoxifen) on the growth of MCF-7Ca breast tumor xenografts in female ovariectomized athymic nude mice



Long, B. J. et al. J. Natl. Cancer Inst. 2004 96:456-465

Letrozole and tamoxifen in MCF-7Ca breast tumor xenografts (Summary)

- Letrozole induced marked regression of MCF-7Ca tumors (tumor volume reduced by 54% over first 4 weeks of treatment!)
- Tamoxifen treated tumors did not regress but tumor growth delayed compared to vehicle (control) for the first 8 weeks

Long, B. J. et al. J. Natl. Cancer Inst. 2004 96:456-465

“Of Mice and WoMen”: Tamoxifen Metabolism

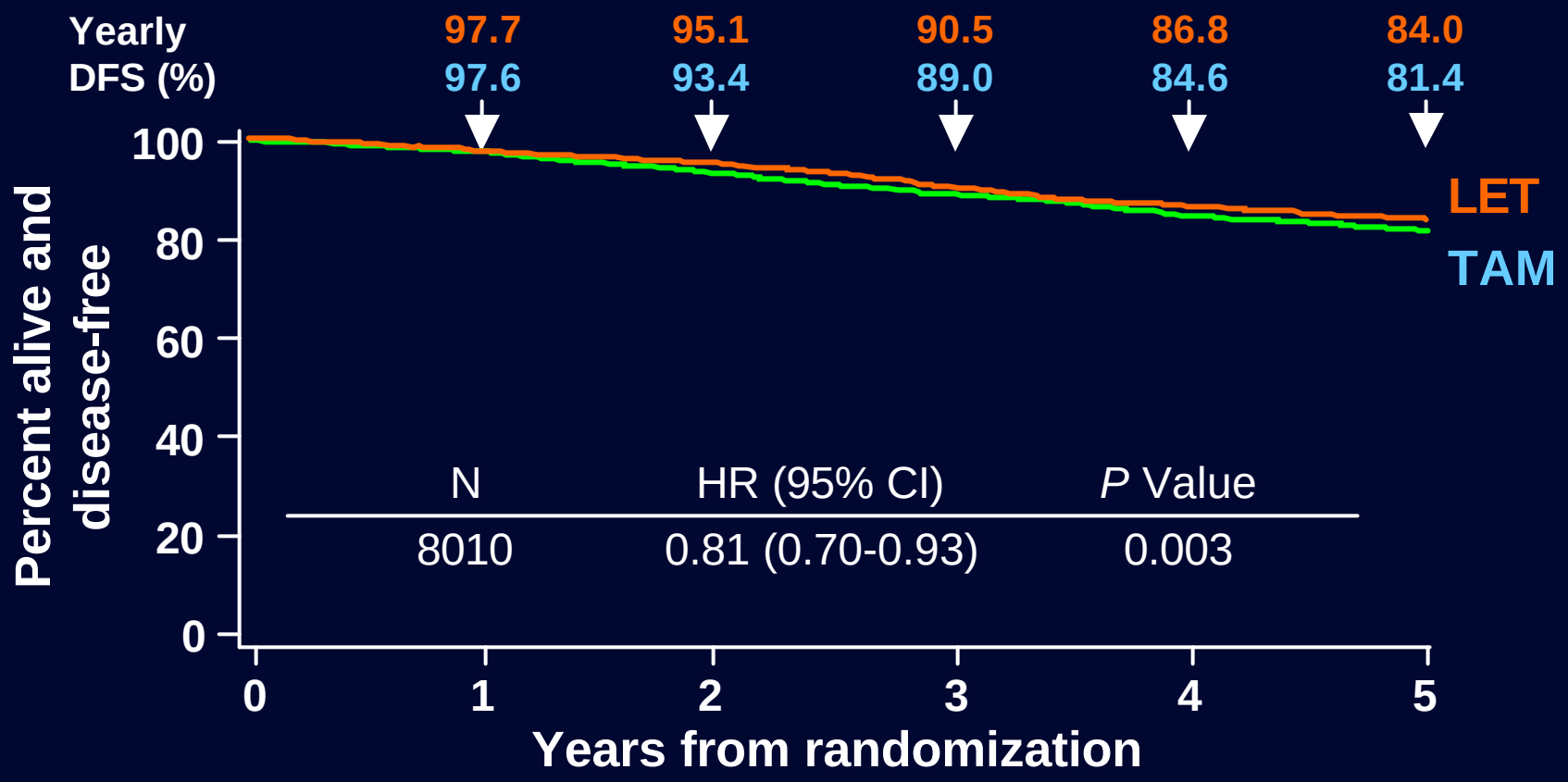
- Did this mouse model predict what happened in the clinic???

Tamoxifen (Clinical Response)
(Metastatic First-line ER +/ER unknown)

	Anastrozole	Tamoxifen
Total	N=328	N=328
Complete Response	5.6%	4.9%
Overall Response rate (CR + PR)	32.9%	32.6%

Bonneterre et al. J Clin Oncol 2000

Disease-Free Survival



HR = hazard ratio; CI = confidence interval.

Thurlimann et al. *J Clin Oncol*. 2005;23(16S):6s. Abstract 511.

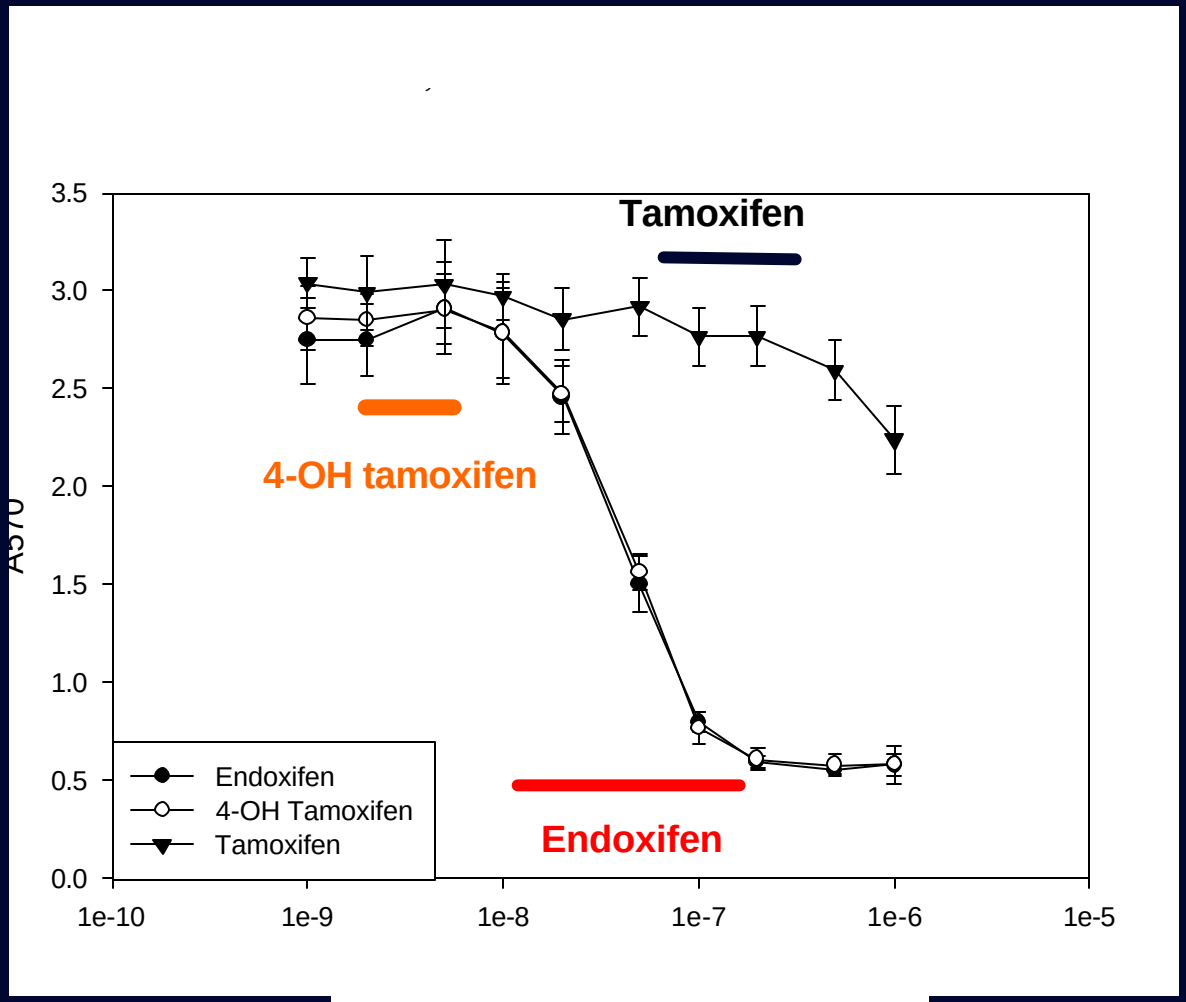
Tamoxifen:

- How can a drug perform so poorly in the laboratory and yet save more lives than any other drug in the history of breast cancer?

Tamoxifen pharmacokinetics (2008)

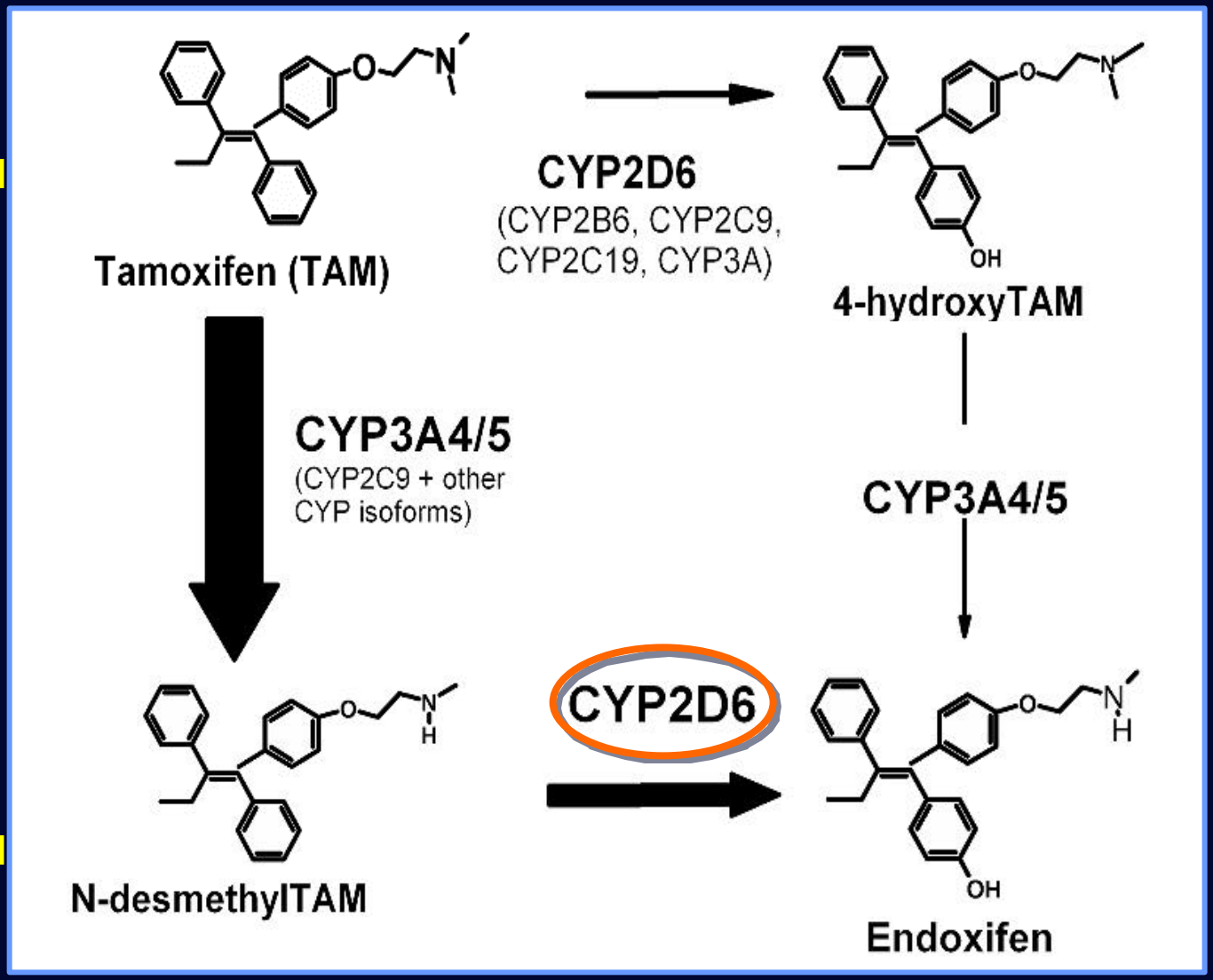
- Not all tamoxifen metabolites are created equal
- Tamoxifen metabolites exhibit marked differences in
  1) ER binding
  2) Inhibition of cell proliferation
- CYP2D6 genetic and drug-induced variation influences drug effect (toxicity and side effects)

Endoxifen and 4-OH-Tamoxifen are Equipotent as Inhibitors of Estrogen Stimulated Cell Proliferation



Johnson MD, et al: Breast Cancer Res Treat 85:151-9, 2004

Tamoxifen Metabolic Pathway (Humans)



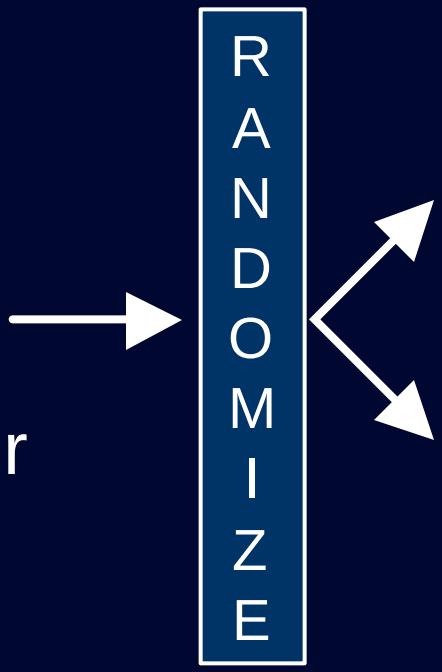
Jin Y et al: J Natl Cancer Inst 97:30, 2005

NCCTG 89-30-52

Postmenopausal women

Early stage

ER$^+$ breast cancer



5 years of tamoxifen (n=256)

5 years tamoxifen + 1 year fluoxymesterone (n=285)

Ingle et al. Breast Cancer Res Treat. 2006; 98:217-222.

CYP2D6*4 Genotyping

- Tamoxifen monotherapy arm (256 patients)

  Formalin-fixed paraffin-embedded tumor blocks (223 patients)

- CYP2D6*4 (n=190)

  Wt/Wt – 137 (72%)

  Wt/*4 – 40 (21%)

  *4/*4 – 13 (7%)

Goetz, Rae J Clin Oncol 23:9312, 2005

Methods

- 225 Charts were reviewed at each randomizing site to ascertain medication history

  Potent CYP2D6 inhibitors: Fluoxetine and paroxetine

  Weak CYP2D6 inhibitors: Sertraline, cimetidine, amiodarone, doxepin, ticlopidine, or haloperidol

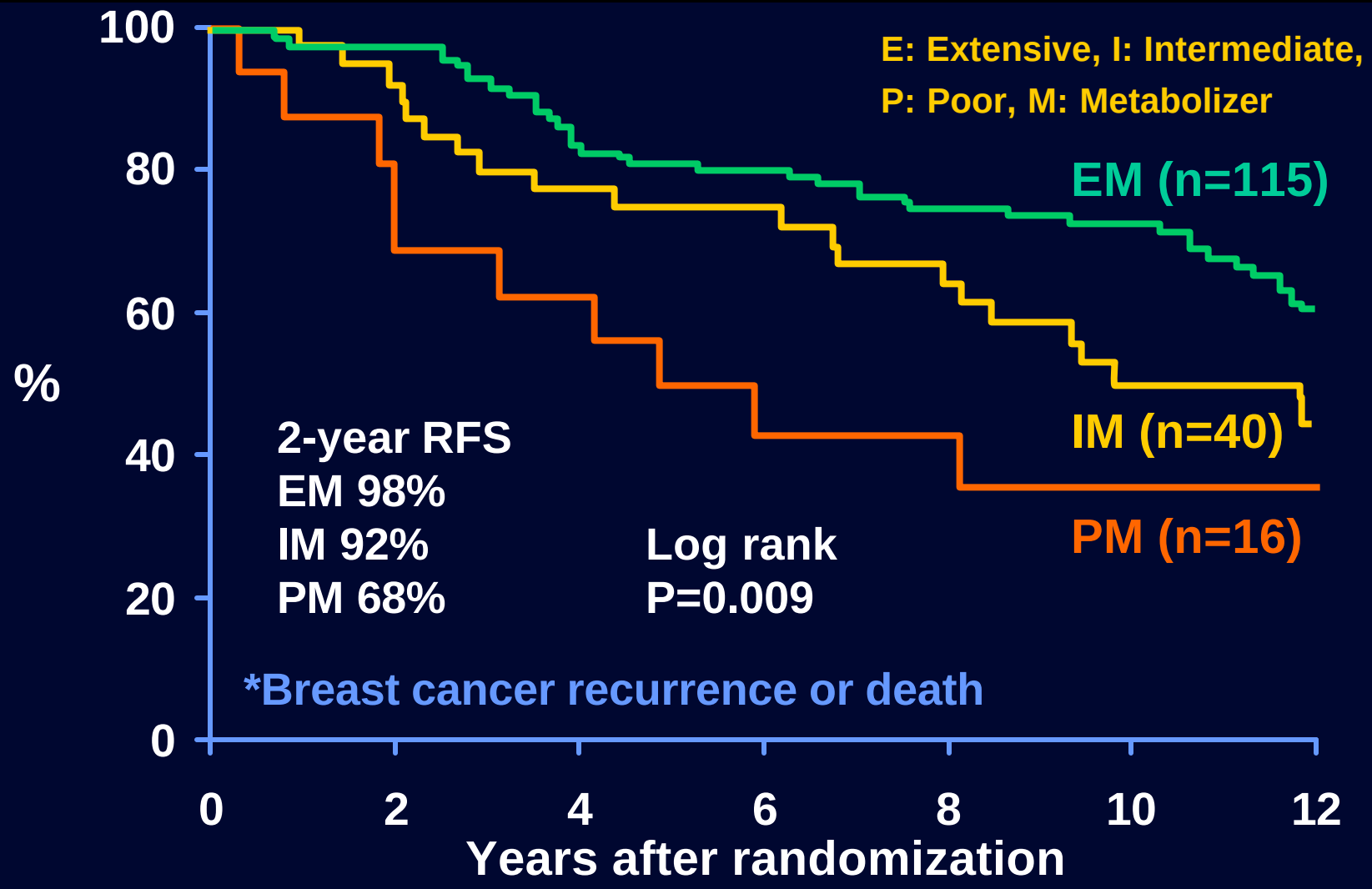
  Duration of coadministration: <1, 1-2, 2-3, 3-4 and 4-5 years

- Statistics: Log rank test and Cox modeling

Metabolizer Status According to CYP2D6 Genotype and Enzyme Inhibition

- Extensive metabolizers: (n=115, 67%)
  - Wt/Wt and no inhibitor
- Intermediate metabolizers: (n=40, 23%)
  - Wt/*4 and no inhibitor (n=32)
  - Wt/Wt and weak inhibitor (n=8)
- Poor metabolizers: (n=16, 9%)
  - *4/*4 (n=13)
  - Wt/Wt and potent inhibitor (n=1)
  - Wt/*4 and potent inhibitor (n=1)
  - Unknown genotype and potent inhibitor (n=1)

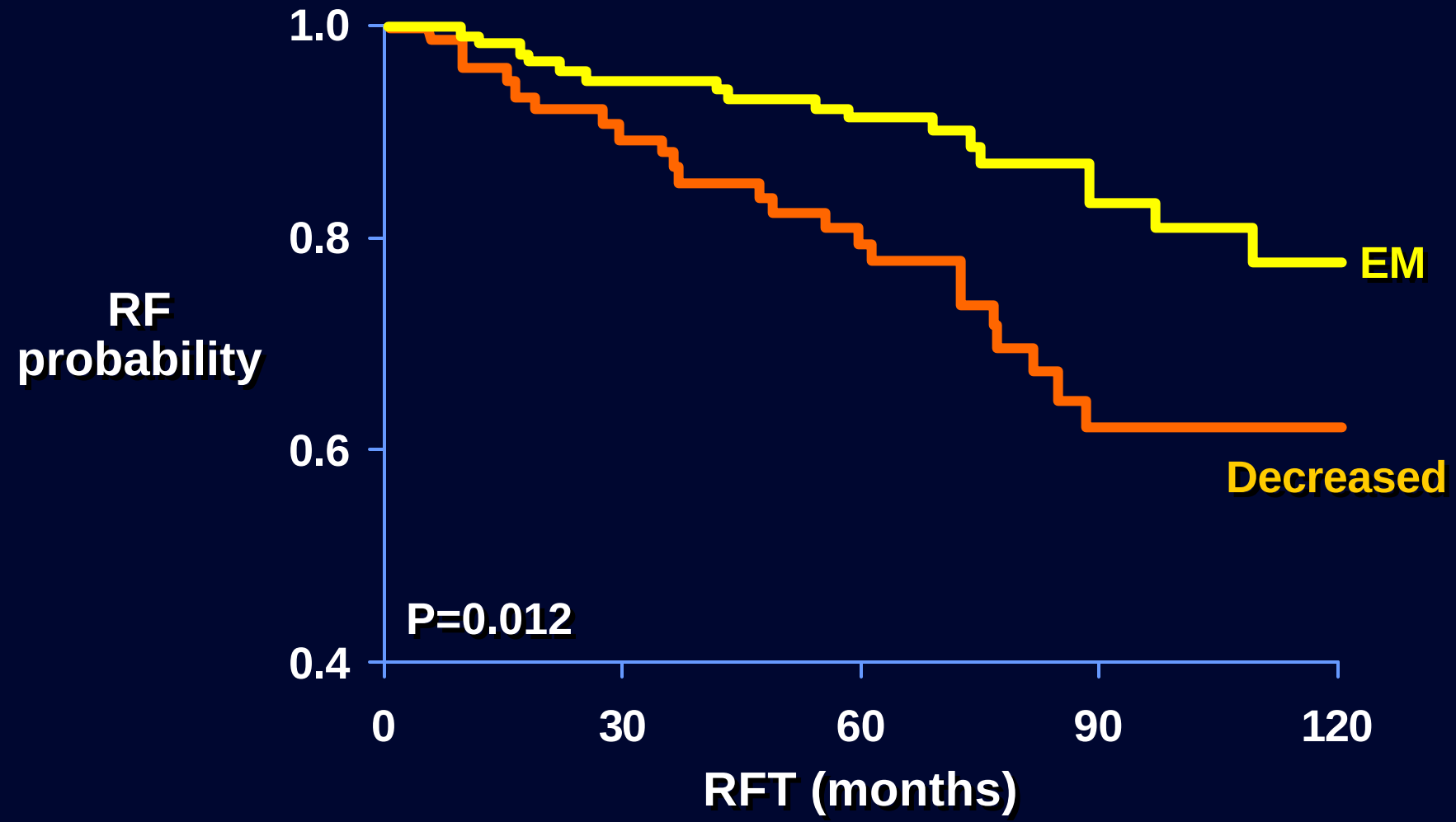
Relapse-Free Survival* According to CYP2D6 Metabolizer Status in Women Receiving Tamoxifen Adjuvant Therapy



Goetz et al J Clin Oncol. 2005;23(36):9312-8.
Goetz M et al. Breast Cancer Res Treat 101:113-121, 2007

Relapse-Free Time for CYP2D6 Metabolizer Status

Monotherapy with Tamoxifen



Schroth et al. J Clin Oncol 2007

CYP2D6 and Tamoxifen in Premenopausal Breast Cancer

- **Adjuvant:**
  - **10-fold higher risk for recurrence in patients with the *CYP2D6 *10/*10* genotype compared with *CYP2D6 *1/*1***
- **Metastatic:**
  - **Time to progression shorter in those carrying *CYP2D6*10/*10* than for others (5.0 v 21.8 months, P = .0032)**

1) Kiyotani et al. Canc Sci 2008

2) Lim et al. J Clin Oncol 2007

Are drug-related side-effects pharmacologically important?

- Hot Flashes are the most common side-effect of tamoxifen
- 70-80% of patient experience hot flashes
- Moderate or severe hot flashes can lead to non-compliance

Incidence of Moderate or Severe Hot Flashes

Genotype	% of patients who developed moderate or severe hot flashes
*CYP2D6 *4/*4 (PM)	0%
*CYP2D6 *4/WT or Wt/WT	20%

Goetz et al J Clin Oncol. 2005;23(36):9312-8.

Tamoxifen, hot flashes and recurrence in breast cancer: Hot flashes predict favorable outcome

Joanne E. Mortimer, Shirley W. Flatt, Barbara A. Parker, Ellen Gold,
Linda Wasserman, Loki Natarajan,
and John P. Pierce
for the WHEL Study Group

Patient Outcomes
after 7.3 years

	Breast cancer Events
Hot flashes	12.9%
NO hot flashes	21%

p=0.01

ATAC: Analysis of outcomes by hot flashes

- Hot flushes were reported in 35% of the women at 3 months (36% anastrozole vs 41% tamoxifen
- Those reporting hot flushes had significantly lower recurrence rates than those who did not (HR 0.74, 95% CI 0.64-0.85, P<0.001)
- Effect seen in both treatment arms (anastrozole: HR=0.66, 95% CI 0.53-0.83, P<0.001; and tamoxifen: HR=0.77, 95% CI 0.64-0.93, P=0.006).

Cuzick, J SABC 2007

Cytochrome P450 2D6 Activity Predicts Adherence to Tamoxifen Therapy

Rae JM, Sikora MJ, Henry NL, Li L,
Kim S, Oesterreich S, Skaar T, Nguyen AT, Desta Z, Storniolo AM, Flockhart DA, Hayes DF, and Stearns V

Consortium on Breast Cancer Pharmacogenomics (COBRA)

PGRN

University of Michigan Medical School

CYP2D6 Poor Metabolizers are Most Likely to Adhere to Tamoxifen

Score	Phenotype	#	Stayed on N (%)	Dropped out N (%)
0	PM	10	10 (100)	0 (0)
0.5	IM	15	14 (93.3)	1 (6.7)
1	IM	72	65 (90.3)	7 (9.2)
1.5	EM	50	43 (86)	7 (14)
2	EM/UM	120	107 (89.2)	13 (10.8)
	Total	267	240 (89.9)	28 (10.5)

Rae, JM SABC 2007

Principles of biomarker discovery and validation (Biomarker 101)

- **Do I need to worry about compliance?**
  - **Tamoxifen: 35% discontinue tam by year 3.5[1]**
  - **Anastrozole: Up to 50% are "non-adherent" by the third year[2]**
- **What happens when researchers are "naïve" to drug compliance during tumor biomarker discovery or validation in the setting of an orally administered therapy**
  - **you "discover" a prognostic factor associated with tumor biology NOT a predictive factor associated with response to the oral therapy**

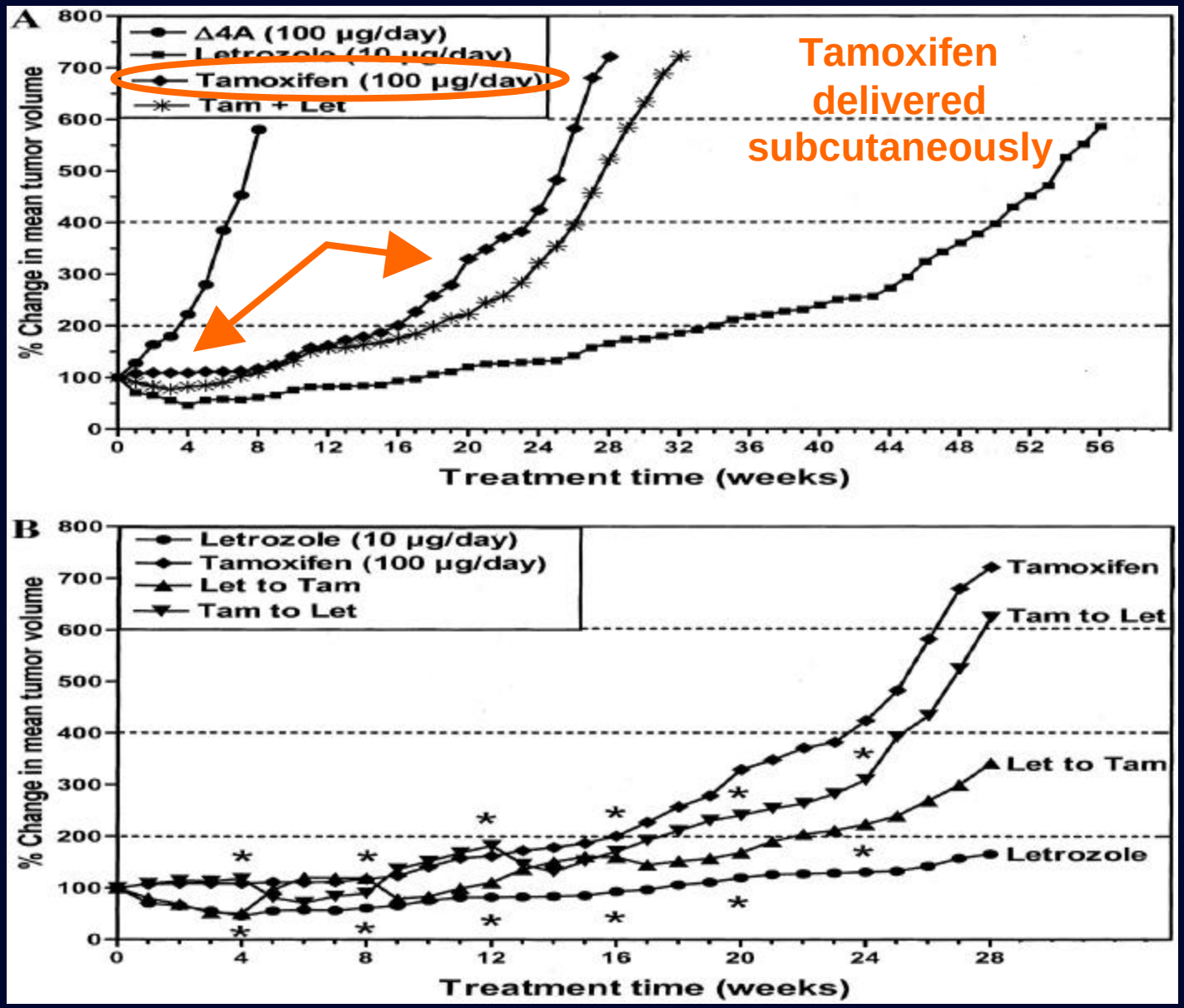
1) Baron et al. Cancer 2007

2) Partridge et al. J Clin Oncol 2007

“Of Mice and WoMen”: Tamoxifen Metabolism

- Why have the pre-clinical models failed to predict what happened in the clinic???

Effects of letrozole and tamoxifen) on the growth of MCF-7Ca breast tumor xenografts in female ovariectomized athymic nude mice



Long, B. J. et al. J. Natl. Cancer Inst. 2004 96:456-465

Tamoxifen Metabolism: How do Mice and Women differ?

- **Tamoxifen metabolism in Mice:**
  - **At 50-100 ug/day[1,2], no serum or tissue tamoxifen, 4-OH or N-desmethyl (endoxifen) metabolites**
  - **2,000 ug/day—tissue concentrations of tam adequate but no endoxifen**
- **Mice do not carry functional CYP2D6 genes and thus serve as a natural knockout for CYP2D6.**

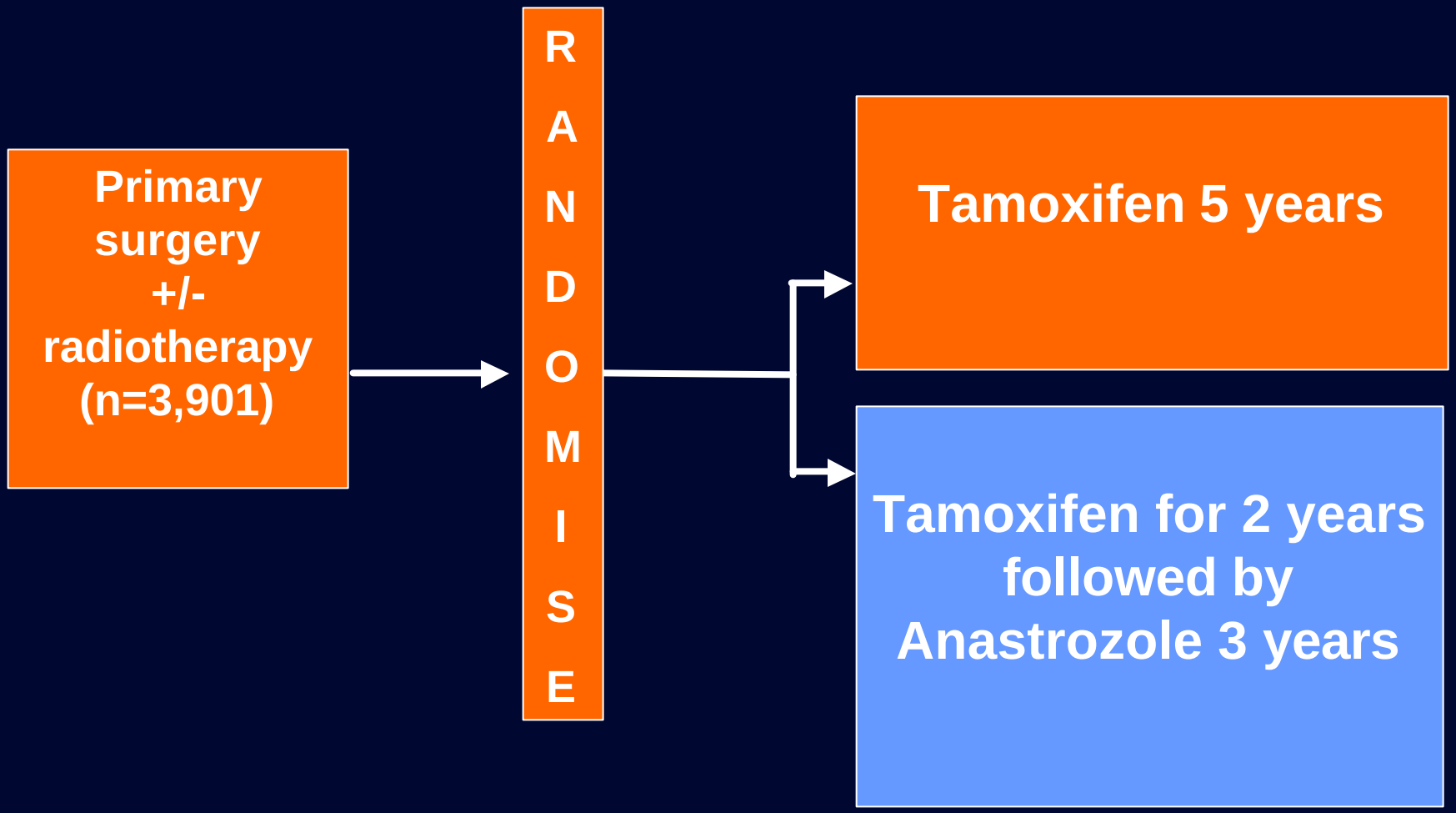
1) Robinson SP, Jordan VC: Drug Metab Dispos 19:36-43, 1991

2) Kisanga ER, Lien E: J Steroid Biochem Mol Biol 84:361-7, 2003

Future Research

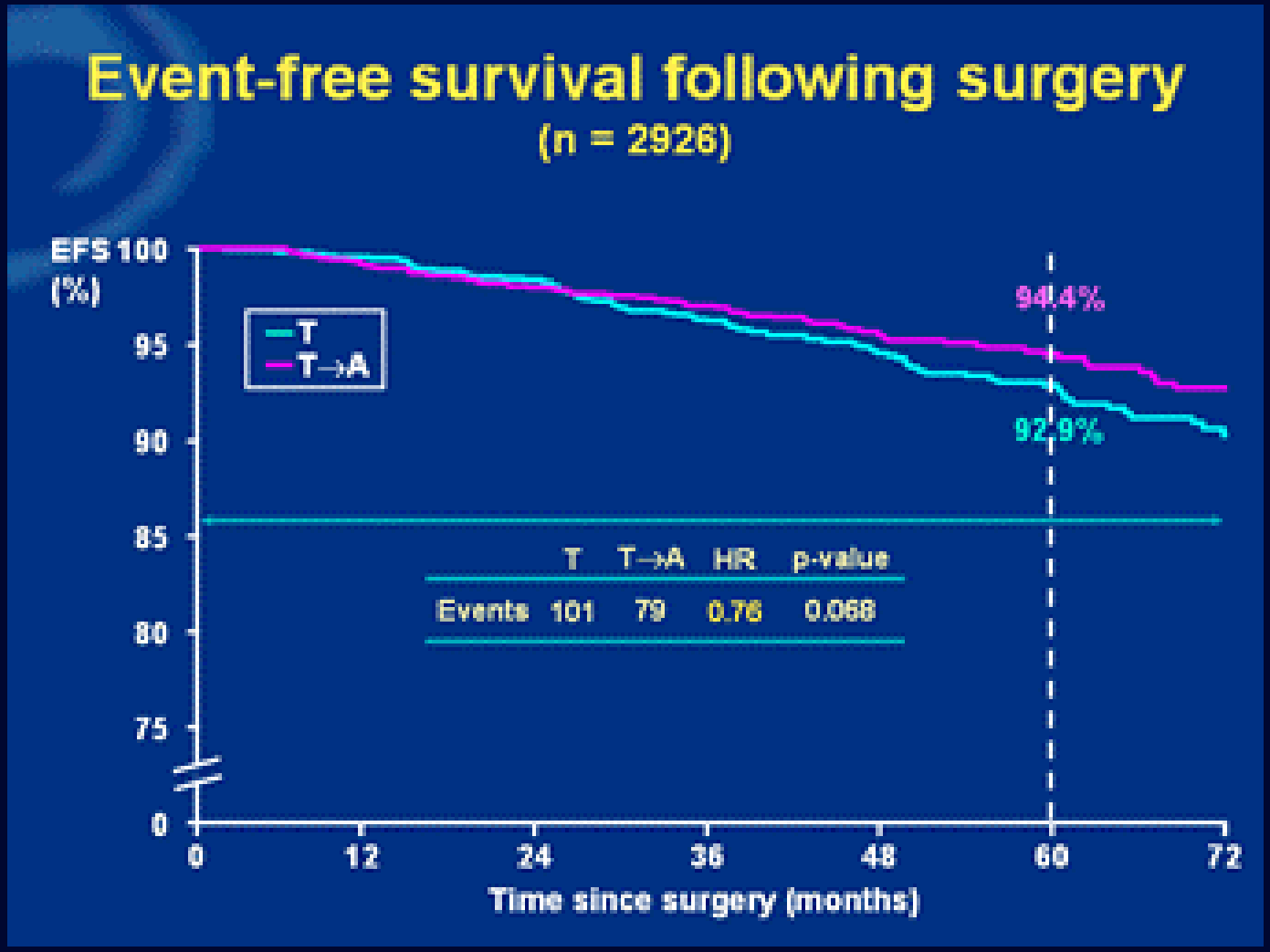
- Does the mechanism of action of endoxifen differ from tamoxifen/4-OH tam (SERM)
- The role of CYP2D6 in the switching of tamoxifen to aromatase inhibitors (Postmenopausal breast cancer)
- Plasma endoxifen levels as a predictor of breast cancer recurrence

ABCSG 8: trial design



Jakesz R et al. Lancet (2005)

ABCSG Trial 8



ABCSG Trial 8

- The benefit of switching: Do some benefit more than others? Could switching be beneficial solely based on principles of pharmacologic exposure to the active metabolite(s)?
- ABCSG trial 8: Case control study

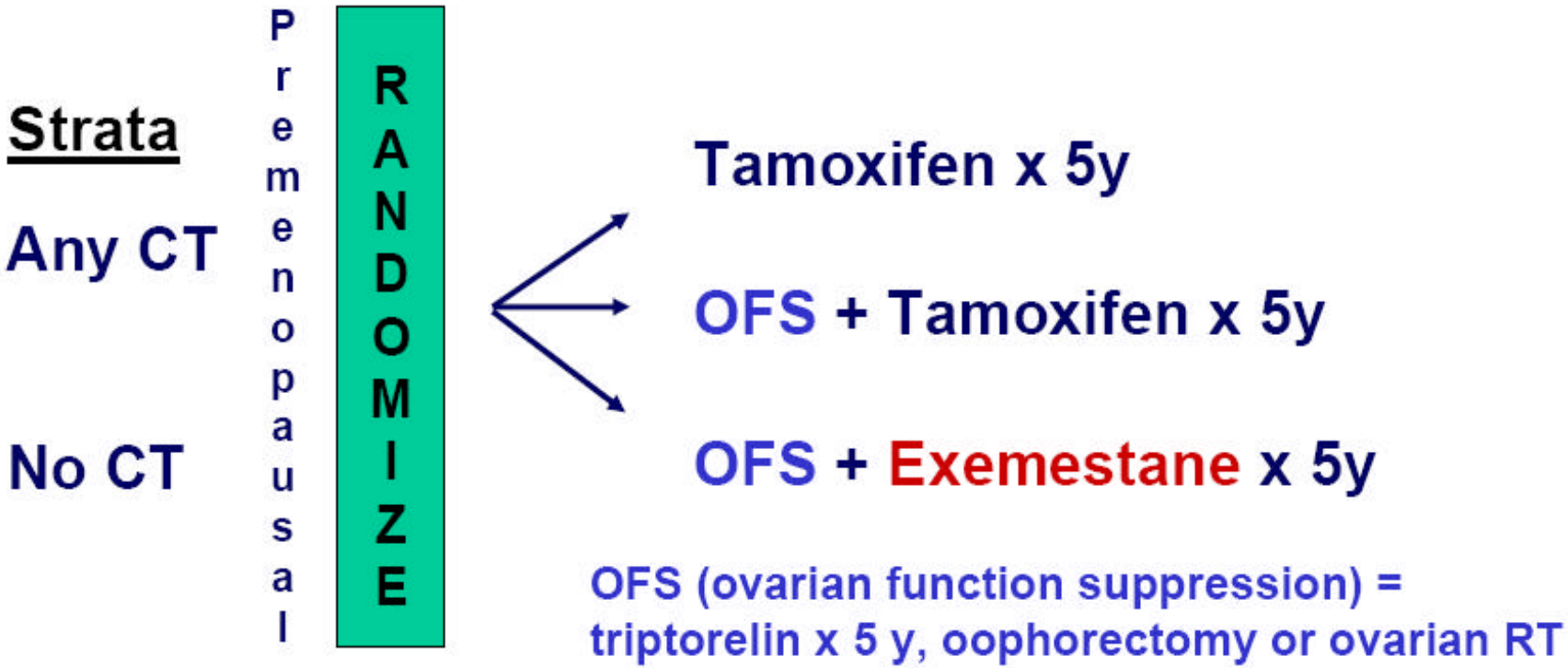
  Tamoxifen only arm:

  Tamoxifen followed by AI:
- Germline: CYP2D6, SULT1A1, others
- Somatic: ER, PR, HER-2, HOXB13/IL17BR, others

SOFT [BIG 2-02, IBCSG 24-02]

Premenopausal, ER and/or PgR ≥ 10%

Patients who remain premenopausal within 8 months after CT, or receive tamoxifen alone as adequate treatment



Target sample size: 3000 patients

Pharmacogenetics: The future is NOW

- Individual practitioners already have access to gene sequence information for their patients
- The proper application of this information will ultimately improve patient outcomes